TSE: Regulatory Aspects in the U.S.

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Bovine Materials in FDA-Regulated Medical Products

- **Scope of products**
  - **Drugs**
  - **Biologics (blood products, vaccines)**
  - **Devices**

Bovine Materials in FDA-Regulated Medical Products

- Types of use (examples)
  - Product (e.g. collagen, bovine thrombin, bovine aprotonin, gelatin)
  - Reagents for cell culture for vaccines, monoclonal antibodies, monoclonal proteins
    - Fetal bovine serum, bovine serum albumin, bovine insulin, etc.
  - Manufacturing reagents (e.g. Polysorbate 80, Tween, lactose, glycerol, amino acids)
  - Reagents for in vitro diagnostics

CBER's Policy Regarding the Sourcing of Bovine-derived Materials

"[T]hat manufacturers … assure that materials derived from all species of ruminant animals born, raised, or slaughtered in countries where BSE is known to exist, or countries where the USDA has been unable to assure FDA that BSE does not exist, are not used in the manufacture of FDA-regulated products intended for administration to humans."

[April, 2000, CBER Letter to Manufacturers of Biological Products]

CBER's Policy Regarding the Sourcing of Bovine-derived Materials

- May, 1991, CBER Letter to Manufacturers
- December, 1993, FDA Letter to Manufacturers
- May, 1996, FDA Letter to Manufacturers
- September, 1997, FDA Guidance for Industry on the Sourcing and Processing of Gelatin
- April, 2000, CBER Letter to Manufacturers of Biological Products
- May, 1993, Points to Consider in the Characterization of Cell Lines used to produce Biologics

Canadian BSE Cow

- Dairy cow imported from Canada with 81 other cattle
- Age: 6.5 years
- Deemed a “downer cow,” unable to walk at slaughter

Canadian BSE Cow

- CNS tissues sent for pathology as part of surveillance program (National Veterinary Services Laboratory, USDA)
- Born prior to mammalian feed ban in U.S. or in Canada (1997)
- 1/~22,000 tested “downer” cattle in surveillance program

U.S. BSE Cow

- December 23, 2003 – diagnosis (Ames, Iowa, NVSL, USDA) based on histopathology and immunohistochemistry; part of surveillance effort by USDA
- December 25, 2003 – diagnosis confirmed, International Reference Laboratory, Weybridge, U.K.
- Immediate actions
  - Quarantine recent source herd
  - Recall beef products
  - Tracing of infected cow to birth cohort

USDA Proposed Rule re: Canada

- **USDA proposed rule [October 31, 2003; http://www.aphis.usda.gov] to allow for, *inter alia*, import of:**
  - **Bovine animals less than 30 months of age for immediate slaughter**
  - **Fresh meat from carcasses of bovines less than 30 months of age; specified organs/tissues**
  - **USDA will review comments as it makes any final decision on the importation of certain live ruminants and ruminant products from Canada and other minimal risk regions for BSE.**

USDA Interim Rule
January 12, 2004
Authority: Federal Meat Inspection Act
Federal Register Volume 69 (7): 1862-1874

- **Specified Risk Material (SRM) removal from cattle 30 months or older**
  - **Brain, skull, eyes, trigeminal ganglia, spinal cord, dorsal root ganglia, vertebral column (except tail, transverse processes thoracic and lumbar vertebrae, wings of sacrum)**
- **SRM removal from ALL cattle**
  - **Tonsils and distal ileum small intestine [entire small intestine to ensure complete removal]**

USDA Interim Rule January 12, 2004

Federal Register Volume 69 (7): 1862-1874

- **All establishments required to**
  - **Develop, implement, maintain written procedures for removal, segregation, disposal SRM's**
  - **Incorporate procedures into HACCP (Hazard Analysis and Critical Control Points) plans or in sanitation SOP's.**
  - **Corrective actions required when identified by establishment or FSIS (Food Safety and Inspection Service)**
  - **Periodic evaluation of effectiveness of measures; maintenance of records for inspection**

USDA Interim Rule January 12, 2004

Federal Register Volume 69 (7): 1862-1874

- **Disposition of "Downer Cows," (regulatory definition: "Non-ambulatory disabled cattle")**
  - **All such cattle must be condemned**
  - **All-inclusive, regardless of apparent cause of injury/illness**
  - **Disposal by inedible rendering (tanking), incineration, or by FSIS-specified chemical methods.**

USDA Interim Rule January 12, 2004

Federal Register Volume 69 (7): 1862-1874

- **Mechanically separated beef banned for use in human food**
- **Bone marrow in meat from Advanced Meat Recovery (AMR) systems will be limited (as detected by iron as a marker)**
- **AMR products continue routine sampling surveillance for presence of spinal cord and dorsal root ganglia tissue (FSIS directive 8/2003)**

Additional Measures

- Enhanced enforcement of feed ban
- Prohibition of certain stunning devices
- Age verification for cattle (records; dentition)
- Institution of a national cattle identification program, announced by USDA on December 30, 2003

Potential Strategies for Minimizing Risk of BSE exposure (1)

- Herd sourcing
  - Previous paradigm – BSE free countries
  - Potential for non-geographic definition of safe sourcing
- Prevention of high-risk tissue contamination of low-risk tissue (harvesting technique)
- TSE clearance by manufacturing processes
  - Risk assessment
  - Process validation for specific conditions

Potential Strategies for Minimizing Risk of BSE exposure (2)

- **Changing to non-animal sourced manufacturing reagents, for example:**
  - **Serum-free media for cultures**
  - **Replacement with plant-derived substances**
  - **May be costly/take time/prove difficult in some instances**
  - **Not feasible for some licensed products (e.g. vaccines)**
  - **May be more feasible during product development**

Potential Strategies for Minimizing Risk of BSE exposure (2)

- Continuing to source from BSE-free countries
  - Diminishing availability
- Appropriate use of products
- Risk communication (labeling strategies)

FDA Actions

- Bovine materials from BSE countries not used in manufacturing [prior to U.S. BSE]
- FDA retains updated lists of bovine materials used in products
- FDA has encouraged manufacturers to switch from bovine-derived materials where possible

Additional FDA Actions

- **FDA research: methods of removing/inactivating TSE's from surfaces**
- **TSEAC review of facility cleaning methods (TSE clearance) 7/18/03**
- **Reevaluation of policies in light of recent vCJD presumptive transfusion transmission and U.S. BSE: TSEAC February 12-13, 2004**

Summary of TSEAC February 12-13, 2004

http://www.fda.gov/cber/advisory/tse/tse0204.htm

- **Informational presentations on risk of transfusion-transmission of vCJD**
- **Update on BSE in the U.S.**
- **Models for risk-based sourcing of bovine materials in FDA-regulated medical products**
- **Discussion on minimizing risks of TSE agents in FDA regulated medical products**

Biologicals and North American Sourced Bovine Materials

- Bovine-derived materials from cattle that are “born, raised, or slaughtered” in the U.S. and Canada are used in U.S.-licensed biologicals as well as those products under development.
- CBER has not requested that biologic manufacturers replace existing Canadian or U.S. sources of bovine-derived material at this time.

The Policy is Clear, But …

Source country control can be problematic when new countries are added to the list:

- **Licensed products remain on the market**
- **Manufacturing time-lines are long (> 1 year)**
- **The status of master cell and seed banks, as well as working cell and seed banks, become unclear; re-derivation and re-qualification takes time**
- **The status of products in development becomes unclear**
- **Risk – benefit decisions continue to be needed**